Bioabsorbable Coronary Stents

John A. Ormiston, MBChB; Patrick W.S. Serruys, MD, PhD

Percutaneous coronary intervention (PCI) with bioabsorbable stents has created interest because the need for mechanical support for the healing artery is temporary, and beyond the first few months there are potential disadvantages of a permanent metallic prosthesis. Stents improve immediate outcomes, including profoundly reducing acute vessel occlusion after PCI by scaffolding intimal tissue flaps that have separated from deeper layers and by optimizing vessel caliber. They limit restenosis by preventing negative remodeling. The separated from deeper layers and by optimizing vessel caliber. They limit restenosis by preventing negative remodeling. The intimal hyperplastic healing response to PCI that contributes to restenosis, especially after bare metal stenting, can be limited by coating stents with antiproliferative medications. Potential advantages of having the stent disappear from the treated site include reduced or abolished late stent thrombosis, improved lesion imaging with computed tomography or magnetic resonance, facilitation of repeat treatments (surgical or percutaneous) to the same site, restoration of vasomotion, and freedom from side-branch obstruction by struts and from strut fracture-induced restenosis. Bioabsorbable stents have a potential pediatric role because they allow vessel growth and do not need eventual surgical removal. The progression of stenosis seen within stents 7 to 10 years after stenting has been attributed, at least in part, to inflammation around metallic struts, which might argue for an absorbable stent. Progression is also observed late after balloon angioplasty. Some patients say they prefer an effective temporary implant rather than a permanent prosthesis.

Although the concept of bioabsorbable stents has created interest for >20 years, there are challenges in making a stent that has sufficient radial strength for an appropriate duration, that does not have unduly thick struts, that can be a drug delivery vehicle, and where degradation does not generate an unacceptable inflammatory response. We will review the different bioabsorbable stents that have been studied clinically and discuss the duration of the need for mechanical support and the potential amelioration of late stent thrombosis risk.

Igaki-Tamai Bioabsorbable Stent

The Igaki-Tamai stent (Igaki Medical Planning Company, Kyoto, Japan), the first absorbable stent implanted in humans, is constructed from poly-L-lactic acid (PLLA). In the absorption process, hydrolysis of bonds between repeating lactide units produces lactic acid that enters the Krebs cycle and is metabolized to carbon dioxide and water. The stent design is a zig-zag helical coil with straight bridges (Figure 1). Strut thickness is larger than that in contemporary metallic stents at 170 μm, and vessel coverage by stent struts (24%) is greater than that with contemporary metallic stents (Table). This balloon-mounted self-expanding sheathed system where expansion is hastened by dilatation with warmed contrast medium is cumbersome to use. As PLLA is radiolucent, gold markers at each end provide radio-opacity for stent identification. The stent does not release an antiproliferative drug. Absorption is by bulk erosion, where absorption occurs throughout the mass of the implant and not just at the surface. This allows the stent strut to retain its shape until absorption is well advanced. In the preliminary, first-in-man prospective, nonrandomized clinical trial that enrolled 50 patients, a 4-year follow-up of all the patients (100%) revealed a low complication rate with 1 in-hospital stent thrombosis causing a Q-wave myocardial infarction, 1 noncardiac death, and 18% repeat PCI and no surgical revascularization. Although there have been no further human coronary implants and the focus is now on a peripheral application, this stent is important in the history of PCI with absorbable stents.

A Bioabsorbable Magnesium Stent

The first metallic bioabsorbable stent implanted in humans is the magnesium alloy stent studied in the Clinical Performance and Angiographic Results of Coronary Stenting with Absorbable Metal Stents trial. This stent, laser cut from tubular magnesium WE-43 (Biotronik, Berlin, Germany), has sinusoidal in-phase hoops linked by straight bridges (Figure 2). It is balloon expandable, with strut thickness of 165 μm, and the 3-mm stent has a crossing profile of 1.2 mm compatible with a 6F guide catheter (Table). The coverage of arterial wall by the expanded stent is similar to that of the conventional metallic stents (10%). The radial strength at implantation is similar to that of stainless steel stents. As the stent is radiolucent and does not have radio-opaque markers, accurate postdilatation and additional stent placement without gaps or long overlap may be a challenge. Absorption is by surface erosion, such that strut thickness decreases as the stent is absorbed.

The Clinical Performance and Angiographic Results of Coronary Stenting with Absorbable Metal Stents trial is a prospective, nonrandomized study where 71 magnesium
stents, 10 to 15 mm in length, were implanted in 63 patients with simple de novo native coronary artery lesions. The immediate angiographic results were similar to those after deployment of other metallic stents. Although the stent was completely absorbed within 2 months, radial support was lost much earlier so that, perhaps within days, there was an insufficient radial strength to counter the early negative remodeling forces after PCI. In addition, it did not release an antiproliferative drug to counter the intimal hyperplastic response to stenting. Consequently, there was a high restenosis rate at 4 months of almost 50% and target vessel revascularization at 1 year was 45%. There were no deaths, myocardial infarctions, or stent thromboses, and the stent was no longer detectable by intravascular ultrasound (IVUS). Although the authors concluded that the magnesium stent could be safely degraded by 4 months, the high restenosis rate may raise concerns about safety. Newer designs explore prolongation of radial support and potential for drug coating.

### BVS Everolimus-Eluting Bioabsorbable PLLA Stent

The BVS everolimus-eluting stent (Abbott Vascular, Santa Clara, Calif) is the first bioabsorbable stent to have clinical and imaging outcomes similar to those following metallic drug-eluting stent (DES) implantation for 2 years but with the potential advantages of full-stent absorption. This stent has a bioabsorbable polymer backbone of PLLA with a polymer coating of poly-D,L-lactide that contains and controls the

#### Table. A Comparison of the Properties of 5 Absorbable Stents and 2 Permanent DES Systems

<table>
<thead>
<tr>
<th>Stent</th>
<th>Strut Material</th>
<th>Coating Material</th>
<th>Design</th>
<th>Absorption Products</th>
<th>Drug Elution</th>
<th>Stent Radial Opaque</th>
<th>Deployment</th>
<th>Total Strut Thickness (μm)</th>
<th>Crossing Profile, mm</th>
<th>Stent-to-Artery Coverage, %</th>
<th>Duration Radial Support</th>
<th>Absorption Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Igaki-Tamai</td>
<td>Polymer-poly-L-lactic acid</td>
<td>Nil</td>
<td>Zip-zag helical coils with straight bridges</td>
<td>Lactic acid, CO₂, and H₂O</td>
<td>Nil</td>
<td>Gold markers</td>
<td>Self-expanding and heated balloon</td>
<td>170</td>
<td>?</td>
<td>24</td>
<td>6 mo</td>
<td>2 y</td>
</tr>
<tr>
<td>Bioabsorbable magnesium alloy</td>
<td>Metal-magnesium alloy</td>
<td>Nil</td>
<td>Sinusoidal in-phase hoops linked by straight bridges</td>
<td>Not applicable</td>
<td>Nil</td>
<td>Nil</td>
<td>Balloon</td>
<td>165</td>
<td>1.2</td>
<td>10</td>
<td>Days or weeks</td>
<td>&lt;4 mo</td>
</tr>
<tr>
<td>BVS bioabsorbable vascular solutions</td>
<td>Polymer-poly-L-lactic acid</td>
<td>Side and lock</td>
<td>Cohort A: out-of-phase sinusoidal hoops with straight and direct links; cohort B: in-phase hoops with straight links</td>
<td>Lactic acid, CO₂, and H₂O</td>
<td>Everolimus</td>
<td>Platinum markers</td>
<td>Balloon</td>
<td>156</td>
<td>1.4</td>
<td>25</td>
<td>Cohort A: weeks; cohort B: 3 mo</td>
<td>2 y</td>
</tr>
<tr>
<td>REVA</td>
<td>Polymer-tyrosine-derived polycarbonate polymer</td>
<td>Nil</td>
<td>Amino acids, ethanol, CO₂</td>
<td>Nil</td>
<td>Iodine impregnated</td>
<td>Balloon</td>
<td>200</td>
<td>1.7</td>
<td>55</td>
<td>3 to 6 mo</td>
<td>2 y</td>
<td></td>
</tr>
<tr>
<td>BBI bioabsorbable therapeutics incorporated</td>
<td>Polymer salicylate + linker</td>
<td>Salicylate + different linker</td>
<td>Tube with laser-cut voids</td>
<td>Salicylate, CO₂, and H₂O</td>
<td>Sirolimus salicylate</td>
<td>Nil</td>
<td>Balloon</td>
<td>200</td>
<td>2.0</td>
<td>65</td>
<td>3 mo</td>
<td>6 mo</td>
</tr>
<tr>
<td>Xience V metallic drug-eluting stent</td>
<td>Metal-cobalt chromium</td>
<td>Ranopolymer</td>
<td>In-phase sinusoidal hoops with curved bridges</td>
<td>Nil</td>
<td>Everolimus</td>
<td>Yes</td>
<td>Balloon</td>
<td>96.2</td>
<td>1.085</td>
<td>10.7</td>
<td>Permanent</td>
<td>Permanent</td>
</tr>
<tr>
<td>Cypher metallic drug-eluting stent</td>
<td>Metal-stainless steel</td>
<td>Polyethylene-co-vinyl acetate + polyvinyl butyl methacrylate</td>
<td>Out-of-phase sinusoidal hoops with curved bridges</td>
<td>Nil</td>
<td>Sirolimus</td>
<td>Yes</td>
<td>Balloon</td>
<td>165.2</td>
<td>1.220</td>
<td>12.9</td>
<td>Permanent</td>
<td>Permanent</td>
</tr>
</tbody>
</table>

**Figure 1.** The expanded Igaki-Tamai bioabsorbable stent. It is constructed from poly-L-lactic acid and is a zig-zag helical coil design with straight bridges. Strut thickness is 170 μm, and coverage of the artery by stent is 24%. It does not have a drug coating. Self-expansion is hastened by balloon inflation with heated contrast. It has gold radio-opaque markers at its ends. Reproduced with permission from Wolters Kluwer Health.

**Figure 2.** A bioabsorbable magnesium stent unexpanded in the left panel and expanded in the right panel at different magnifications. It is a laser cut from tubular magnesium WE-43 and has sinusoidal in-phase hoops linked by straight bridges. Strut thickness is 170 μm but crossing profile for the 3.0-mm stent is only 1.2 mm. The arterial coverage by expanded stent is similar to conventional metallic stents at 10%. It is balloon expandable, does not have a drug coating, and is radiolucent.
crease duration of radial support to months but retain the polymer material but different methods of processing in-cohort B of the Absorb trial is constructed from the same thickness of 150 μm and crossing profile of 1.4 mm. These stents are balloon expandable and have platinum radio-opaque markers at each end.

The design of the BVS stent revision 1.0 used in cohort A of the Absorb trial is circumferential out-of-phase zig-zag hoops linked either directly or by straight bridges. Revision 1.1 to be used for cohort B has circumferential in-phase hoops linked by straight bridges. Each, when expanded, covers 25% of arterial wall. It has more uniform vessel coverage and support in addition to higher radial strength. Both revisions have strut thickness of 150 μm and crossing profile of 1.4 mm. These stents are balloon expandable and have platinum radio-opaque markers at each end.

The expanded bioabsorbable BVS stent revisions 1.0 and 1.1. These have struts constructed from poly-L-lactic acid with a poly-D,L-lactic acid coating that contains and controls the release of everolimus. The design of revision 1.0 used in cohort A of the Absorb trial is circumferential out-of-phase zig-zag hoops linked either directly or by straight bridges. Revision 1.1 to be used for cohort B has circumferential in-phase hoops linked by straight bridges. Each, when expanded, covers 25% of arterial wall. It has more uniform vessel coverage and support in addition to higher radial strength. Both revisions have strut thickness of 150 μm and crossing profile of 1.4 mm. These stents are balloon expandable and have platinum radio-opaque markers at each end.

The acute performance of the BVS bioabsorbable stent is similar to that of some metallic stents. The strut thickness and the crossing profile of 1.4 mm are similar to those of the Cypher stent (Cordis, a Johnson & Johnson Company, Miami, Fla). Immediate recoil was similar to that of a cobalt chromium stent.15 Radial strength, measured in a water bath at 37°C by recording with IVUS the cross-sectional area changes occurring with incremental pressure increase was in the same order as that of a Multi-Link stent.10 Although the Multi-Link stent had relatively low radial strength compared with other metal stents, clinical outcomes were very good even with long stents.16

In cohort A of the Absorb first-in-man trial, 3-mm diameter BVS stents either 12 mm or 18 mm in length were implanted in 30 patients with simple, de novo, native coronary artery stenoses. The procedure was a success in all 30 patients, and there was successful delivery of the BVS device in 94% (29 of 31 attempts). In 2 patients, the BVS stent became dislodged—in the first patient, the device was successfully retrieved and a new BVS was implanted without complications, and in the second patient, the BVS stent was implanted in a nontarget lesion and Cypher stents were implanted in the target lesion.8 The device was safe for 2 years with only 1 ischemia-driven major adverse event, which was a non-Q myocardial infarction.11 Interestingly, although at 6 months IVUS revealed no vessel shrinkage (no change in the area within the external elastic lamina), there was reduction of 11% to 12% in the stent area.9 This, in addition to intimal hyperplastic tissue, resulted in a 16.8% reduction in luminal area.

The angiographic late loss of 0.44 mm was similar to that of some metallic DES.9 Although the stent shrinkage raised concerns, the stent had performed its mechanical function of resisting the negative remodeling, which is the main cause of restenosis after balloon angioplasty.1 The antiproliferative drug constrained any excessive healing response; the area obstruction within the stent on IVUS of 5.54% was similar to the 8% observed for the everolimus-eluting Xience V arm at 6 months in the Spirit first trial.9,13 A fascinating finding is that between 6 months and 2 years there was an enlargement of the lumen detected by imaging with IVUS and optical coherence tomography, although there was no change in the angiographic late loss.11 In addition, other remarkable findings in the small number of patients tested are the vasoconstriction induced by methylergonovine maleate and vasodilation induced by nitroglycerin in the “stented” segment.11 This vasoactivity is possible because, with stent absorption, the vessel is no longer splinted by a rigid cage. It raises the possibility of return of a physiological response to vasoactive stimuli, such as exercise and the potential for the artery to dilate in response to local ischemia. It raises the hope that after stent absorption there is a healed vessel that is normally functioning.

**REVA Bioabsorbable Stent**

The REVA (Reva Medical Inc, San Diego, Calif) stent is constructed from an absorbable tyrosine-derived polycarbonate polymer that metabolizes to amino acids, ethanol, and carbon dioxide. The absorption time can be modified. It is balloon expandable with a slide and lock (ratchet) design that allows stent expansion without material deformation (Figure 3).
Bioabsorbable Therapeutics Stent

The bioabsorbable therapeutics stent (Bioabsorbable Therapeutics Inc, Menlo Park, Calif), a fully bioabsorbable sirolimus-eluting stent that also releases salicylic acid, has a polymer backbone that gives the stent the physical structure and a polymer coating that contains and controls the release of the antiproliferative agent (Figure 5).

The structure of the coating polymer is repeating salicylate molecules linked by adipic acid molecules. The stent backbone and coating polymers constructed from repeating salicylate molecules joined by linker molecules. The coating contains and controls the release of sirolimus. The stent has a high stent to artery ratio of 65%. It has a strut thickness of 200 μm and a crossing profile of 2.0 mm. It is balloon expandable and radiolucent.

Bioabsorbable Therapeutics Inc, Menlo Park, Calif, a fully bioabsorbable sirolimus-eluting stent that also releases salicylic acid, has a polymer backbone that gives the stent the physical structure and a polymer coating that contains and controls the release of the antiproliferative agent (Figure 5).

How Long Do Coronary Arteries Need the Mechanical Support of a Stent?

Stents, essential components of contemporary PCI, scaffold intimal flaps that have separated from deeper layers, prevent early constrictive remodeling, and deliver antiproliferative drug to limit excessive healing. After this, a permanent implant is unnecessary and has potential disadvantages. After balloon angioplasty, preclinical and human studies have shown that restenosis is caused mainly by early constrictive remodeling (vessel shrinkage) and to a lesser extent by an inflammatory restenotic response. Prevention of constrictive remodeling is the major reason stents limit restenosis. Over time, during the absorption process, an absorbable stent gradually loses its radial strength and ability to resist constrictive remodeling forces long before it is fully absorbed. What is not clear is how long the artery needs the support of a stent.

In a clinical study using serial angiography and IVUS after angioplasty and directional coronary atherectomy, there was some early positive remodeling up to 1 month and then between 1 and 6 months there was luminal reduction due mainly to negative remodeling (reduction in external elastic lamina). Most angiographic restenosis after balloon angioplasty occurs between 1 and 3 months and is rare thereafter. Absorption of a magnesium alloy stent in humans was rapid and mechanical support lasting days or weeks was too short to prevent constrictive remodeling and restenosis. These data taken together suggest that a mechanically intact stent is needed to counter negative remodeling and limit restenosis for somewhere between 1 and 3 months. Stents are required to limit the constrictive remodeling in the first 6 months after balloon angioplasty. Because most patients have luminal enlargement between 6 months and 5 years after balloon angioplasty, a stent is not needed beyond 6 months. If, as has been postulated but not proven, the late luminal enlargement after balloon angioplasty is due to adaptive positive arterial remodeling, a circumferentially rigid stent may be disadvantageous in that it may obstruct this normal component of vessel healing.
In the Absorb trial, the polyactide BVS stent struts resisted the constrictive remodeling forces sufficiently, such that by 6 months on IVUS there was no vessel shrinkage (no change in external elastic lamina) although the stent itself had reduced in cross-sectional area by 11% to 12%.9 Between 6 months and 2 years, IVUS showed no change in vessel area (external elastic lamina), but the lumen increased in size and the stent was no longer identifiable by 2 years.13 The BVS stent clearly did its job of preventing negative remodeling; however, the duration for which radial support was provided is unclear.

Will Bioabsorbable Stents Eliminate the Risk of Late Thrombosis at the PCI Site?

DES are a major breakthrough in interventional cardiology because they more than halve the need for repeat intervention compared with BMS.25,26 Although a small increase in thrombosis is offset by a reduced risk of complications associated with repeat revascularization,27,28 late (6 month to 1 year) or very late (beyond 1 year) thrombosis is the feared complication of stenting that may result in myocardial infarction and death.27–29 Although late-stent thrombosis occurs with both BMS and DES, that after DES occurs later and as primary thrombosis, whereas that after BMS can be secondary to repeat intervention for restenosis.28,30,31 A worst case scenario is that the problem of late-stent thrombosis after first-generation DES implantation may be ongoing indefinitely as a registry of >8000 patients reported that it occurred at a constant rate of 0.6% per annum without diminution by 4 years.32,33 Indefinite continuation of dual antiplatelet therapy is not a practical solution because of expense and because a quarter of late-stent thromboses occurred in patients receiving dual antiplatelet therapy.32 In addition, dual antiplatelet therapy may be discontinued because of troublesome minor bleeding or to reduce the risk of bleeding during surgery.34–36 An ideal DES would have no risk of late thrombosis and a fully bioabsorbable drug-eluting stent may fulfill this hope. Primary thrombosis at the treated site almost never occurred late after balloon angioplasty and has been described as the bane of stenting from the very beginning.37 Although multiple factors predispose to late thrombosis, it is reasonable to hope that it will be rare if a stent is completely absorbed because there would be no permanent metallic or polymeric foreign body exposed to blood even if endothelialization were functionally abnormal, delayed, or incomplete.38–41 If stent struts disappear, there can be no late stent malapposition. If the stent struts and coating are completely absorbed and the drug gone, there may be none of the ongoing chronic inflammation known to predispose to thrombosis.38,42 The endothelial regrowth after first-generation Taxus or Cypher stenting may be delayed but, in addition, may be functionally abnormal.40,41 Preliminary reports from some patients 2 years after BVS stent implantation raise the possibility of return of a functionally normal endothelium at the stented site because there was vasodilatation or absence of vasoconstriction downstream after acetylcholine administration.11 These observations need to be confirmed in a larger trial.

When the bioabsorbable coating of a metallic DES has been absorbed, all that remains is a BMS, and so the risk of late thrombosis may be limited to that of a BMS.43 However, even BMS have an ongoing risk of thrombosis that may be improved if there were no permanent foreign body in the vessel wall.34–36 An additional reason that a fully bioabsorbable DES may have a low risk of late thrombosis, perhaps lower than even late after balloon angioplasty, is that the antiproliferative drug reduces restenosis and hence the thrombosis associated with repeat intervention.27,28

Summary

An ideal stent should furnish best acute outcomes after PCI by sealing intimal flaps and optimizing lumen size. It should control restenosis by limiting negative remodeling and by controlling excessive healing by delivery of an antiproliferative drug. Beyond 6 months, a permanent implant has no useful function and has possible disadvantages including the potential for late thrombosis.

The concept of a stent that does its job and disappears has appeal.44 A number of different materials ranging from magnesium to a variety of polymers have been used to construct stents of different designs. Some of these are being tested in clinical trials. The best outcomes to date have been with the BVS everolimus-eluting PLLA stent where in the Absorb trial, cohort A at 2 years, the stent was safe in the small number of patients with simple lesions.9,11 Indeed, there is a suggestion of luminal enlargement between 6 months and 2 years, return of vasomotion, and endothelial function. These findings need to be confirmed in larger trials in more complex lesions. A hope is that a healed, normally functioning vessel free of foreign body and restenosis will be free of the risk of late thrombosis. Time will tell if this dream will come true.

Disclosures

Dr Ormiston is a member of the Abbott Vascular and Boston Scientific advisory boards. He is a principal investigator for cohort A and a co-investigator for cohort B of the Absorb Trial, Dr Serruys is a co-principal investigator for cohort A and is a principal investigator for cohort B of the Absorb Trial.

References


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doi: 10.1161/CIRCINTERVENTIONS.109.859173

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